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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,350	07/11/2003	Ranga R. Namburi	27493U	2736

20529 7590 12/04/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
12/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/617,350	NAMBURI ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-13,15-20 and 22-42* is/are pending in the application.

4a) Of the above claim(s) *9-13 and 24-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 15-20, 22-23, and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 8/18/2008, are acknowledged and entered. Claim 21 has been cancelled by Applicant. Claims 1-7, 9-13, 15-20, and 22-42 are pending and under examination.

Claims 9-13 and 24-41 remain withdrawn from consideration. Accordingly, claims 1-7, 15-20, 22-23, and 42 are presently under examination and are the subject of this Office Action.

Response to Arguments

Any previous rejections and/or objections to claim 21 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Applicant's arguments filed 8/18/2008 have been fully considered but they are not persuasive. Applicants present the following arguments.

Independent claim 1 is directed to a method of manufacturing a water-insoluble azole antifungal active agent--oral dosage form, said method comprising the steps of: providing a single phase working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof; providing core particles formed from a pharmaceutically acceptable material; combining said working solution with said particles to produce a water-insoluble azole antifungal active agent-coated particles; drying said water-insoluble azole antifungal active agent -coated particles; and forming said dried particles into an oral dosage form; wherein said working solution is essentially free of methylene chloride, and said oral dosage form is essentially free of methylene chloride.

Gilis et al. teaches a method of manufacturing a water-insoluble azole antifungal active agent--oral dosage form, said method comprising the steps of: preparing a drug coating solution by dissolving into a suitable solvent system appropriate amounts of an antifungal agent and a water-soluble polymer, wherein the solvent system comprises a mixture of methylene chloride and an alcohol (page 9, lines 14-18). In order to reduce residual solvent levels in the drug

coating layer, the drug coated cores can be dried in a microwave vacuum apparatus (page 10, lines 32-33). The reference differs from the instantly claimed method in the composition of the working solution.

Ishibishi et al. relates to sustained release formulations prepared by spray-coating a solution of a hydrophobic organic substance-water-soluble polymer mixture onto a drug-containing core substance. The reference differs from the claims in that a polymeric layer is sprayed on top of a drug-containing core rather than the drug and polymer being present in the same layer as recited in the claims. However, Ishibishi et al. is provided as evidence that a solvent system for coating a particle core which includes alcohols, hydrocarbons, ketones such as acetone, or a mixture of such solvents was known in the art and that such solvent systems should be selected so as to dissolve both the hydrophobic organic compound and the water-soluble polymer (page 6, [0057] and [0058]). Thus, while the particle core being coated differs from the instant claims, the invention of Ishibishi et al. relates to the claimed method in that the coating solution contains both a hydrophobic organic compound and a water-soluble polymer. As such, a solvent system useful in Ishibishi et al. would also be expected to be useful in the presently claimed methods.

Lynenskjold et al. teaches the production of spray-coated particles comprising an inert particulate carrier, a cellulosic binder (e.g., hydroxypropylcellulose), an active substance, and water. Lynenskjold et al. teaches the use of aqueous dispersions or solutions are preferred for the coating composition, but that alcohols (e.g., ethanol), ketones (e.g., acetone), and chlorinated hydrocarbons (e.g., methylene chloride) may also be used, but chlorinated hydrocarbons are not preferred. The reference thus relates to the claimed invention in that a particle core is being coated with a coating solution comprising a water-soluble polymer and a drug substance, which drug may be an antifungal such as ketoconazole (page 4, [0046]). Lynenskjold et al. explicitly suggest that a suitable solvent mixture can comprise water and alcohol (page 3, [0033]).

Nara et al. teaches a drug core coated with a composition comprising a water-insoluble substance, a swellable polymer, and optionally a hydrophilic substance dissolved in a solvent wherein in the solvent can be water, an organic solvent, or mixtures thereof. The organic solvent can be ethyl alcohol or acetone as recited in the instant claims. Water and its mixture with an organic solvent are preferably used as solvent of the coating composition (col. 6, lines 47-48).

Thus, while the particle core being coated differs from the instant claims, the invention of Nara et al. also relates to the claimed method in that the coating solution contains both a hydrophobic organic compound and a water-soluble polymer. As such, a solvent system useful in Nara et al. would also be expected to be useful in the presently claimed methods.

Applicants argue that the pending claims are distinguishable from the cited references because none of the references, taken alone or in combination, contain all the elements of the presently pending in the same working solution. However, contrary to Applicant's assertion, the cited references teach, suggest, and motivate the use of solvent systems comprising water and a solvent selected from alcohols, acetone, and mixtures thereof for the preparation of coating solutions for applying drug substances and water-soluble polymers to core particles. For example, Gilis et al. differs from the claims only in that the solvent system is comprised of methylene chloride and an alcohol, as opposed to water and an alcohol or acetone or mixture thereof. However, the Ishibishi et al., Lynenskjold et al., and Nara et al. references all teach solvent systems for applying coatings to core particles that comprise alcohols, ketones, and/or water. As such, one skilled in the art would reasonably expect that a working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof would be effective to coat core particles. Both Gilis et al. and Lynenskjold et al. provide the motivation to use solvent systems that do not contain chlorinated hydrocarbons wherein Gilis et al. teach that the concentration of dichloromethane in the coated pellets should be less than 600 ppm, preferably less than 300 ppm, and most preferably less than 250 ppm and Lynenskjold et al. teach that chlorinated hydrocarbons are not preferred.

Applicants argue that Gilis et al. and Ishibishi et al. both disclose dichloromethane as a suitable solvent and that Gilis et al. teach that azole antifungal compounds are sparingly soluble in water, and that other non-aqueous based systems must be used in order to solubilize the compounds. However, Lynenskjold et al. teach that antifungals such as ketoconazole can be applied using the solvent systems disclosed therein, which comprise solvent mixtures such as water and alcohol. One skilled in the art would reasonably expect that a compound that is sparingly soluble in water could be dissolved in an aqueous solvent system that further contains one or more co-solvents such as alcohols and/or ketones as suggested by the cited references.

Applicants argue that Ishibishi et al. discloses the use of dichloromethane as a suitable solvent, which is specifically excluded from the presently amended claims. Further, Applicants argue that Ishibishi et al. does not state how to reduce or eliminate the levels of dichloromethane to the extent taught by the present application. In this regard, as discussed supra, Ishibishi et al. is provided as evidence that a solvent system for coating a particle core which includes alcohols, hydrocarbons, ketones such as acetone, or a mixture of such solvents was known in the art and that such solvent systems should be selected so as to dissolve both the hydrophobic organic compound and the water-soluble polymer (page 6, [0057] and [0058]). Thus, while the particle core being coated differs from the instant claims, the invention of Ishibishi et al. relates to the claimed method in that the coating solution contains both a hydrophobic organic compound and a water-soluble polymer. As such, a solvent system useful in Ishibishi et al. would also be expected to be useful in the presently claimed methods.

Regarding the Lynenskjold et al. reference, Applicants argue that the reference does not teach or suggest a combination of water and an organic solvent along with the water soluble polymer. However, contrary to Applicant's characterization of Lynenskjold et al., the reference relates to the claimed invention in that a particle core is being coated with a coating solution comprising a water-soluble polymer and a drug substance, which drug may be an antifungal such as ketoconazole (page 4, [0046]). Further, Lynenskjold et al. explicitly suggest that a suitable solvent mixture can comprise water and alcohol (page 3, [0033]).

Applicants argue that the solvent system of Nara et al. does not include a water-insoluble azole antifungal agent or any other active agent. However, the solvent systems of Nara et al. are taught to be suitable for spray coating particles with a coating composition comprising a water-insoluble substance, a swellable polymer such as the claimed water-soluble polymers. As such, one skilled in the art would reasonably expect the solvent systems of Nara et al. to also be suitable for spray coating particles with a coating composition that contains a water-insoluble drug and a water-soluble polymer. In fact, Nara et al. explicitly suggest that any solvent system can be used in the invention, provided that it dissolves both the hydrophobic organic compound and water-soluble polymer (page 6, [0057]).

Applicants argue that none of the cited references disclose a working solution containing the drug, water-soluble polymer, solvent, and water, wherein the working solution is essentially

free of methylene chloride as recited in the instant claims. While it is true that no individual reference disclose such a working solution, the combination of the cited references suggests and motivates the use of any suitable solvent system for spray coating particles, including solvent systems that contain water, an alcohol, acetone, or mixtures thereof. One of ordinary skill in the art at the time the invention was made would have thus been motivated to try other solvent systems for applying the azole antifungal agents and water-soluble polymers as disclosed in Gilis et al., especially in view of the fact that Gilis et al. teaches that the content of dichloromethane should be less than 600 ppm, preferably less than 300 ppm, and most preferably less than 250 ppm and Lynenskjold et al. teaches that chlorinated hydrocarbons are not preferred in their coating solutions.

Applicants argue that no motivation exists to combine the references and thus cannot render the claims obvious. In this regard, Applicants argue that the cited references fail to teach or suggest all the limitations of the pending claims as required by In re Wilson and that the skilled artisan would have no motivation to modify Gilis et Al. or Ishibishi et al. to incorporate the solvent system of Lynenskjold et al. or the solvent system of Nara et al. Firstly, the combined cited references clearly teach, suggest, and motivate one skilled in the art to use any suitable solvent system for spray coating particles, including solvent systems comprising water, an alcohol, acetone, and mixtures thereof. Determining optimal coating solutions in view of the cited references is well within the purview of the skilled artisan. Secondly, with regard to modifying Gilis et al. or Ishibishi et al. to incorporate different solvent systems, while the solvent systems of Gilis et al. are limited to solvent systems containing dichloromethane, Gilis et al. teaches that the presence of Class 2 solvents such as dichloromethane and methanol should be limited in pharmaceutical products (page 2, lines 23-32), thus motivating one skilled in the art to look for other solvent systems that do not contain dichloromethane and/or methanol. In this regard, the Ishibishi et al, Lynenskjold et al., and Nara et al. all teach and suggest such solvent systems for applying coating solutions to particles, particularly solvent systems comprising water and other co-solvents such as alcohols and ketones. As discussed supra, one of ordinary skill in the art at the time the invention was cuold have readily provided a single phase working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a

solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof for use in coating core particles.

Applicants argue that they have demonstrated unexpected results for the claimed subject matter, referencing the enhanced dissolution and bioavailability of the active ingredient in particles prepared according the pending claims when compared to the commercial product SPORANOX (Table 5). However, Applicants have not described exactly how the itraconazole particles tested in the examples at page 24 were prepared (solvent system, water-soluble polymer, etc.) nor how the commercial SPORANOX particles are prepared. As such, the Examiner is not persuaded that an unexpected result has been demonstrated. Further, the itraconazole particles tested by Applicants are not seen to be commensurate in scope with the patent protection sought by Applicants, which broadly encompasses preparing coated particles using any water-insoluble azole antifungal agent, any water-soluble polymer, and any solvent selected from alcohol, acetone, and mixtures thereof, which may also contain other excipients as recited in the dependent claims.

With regard to claim 7, Applicants argue that there is no motivation to use an amorphous drug as taught by Vladyka et al. in a solution of water-soluble polymer, water, and a solvent to be sprayed onto a core particle. However, Vladyka et al. clearly teach that converting a sparingly water-soluble active agent to its amorphous form results in stabilized solutions of the active agent in aqueous solutions. As such, one skilled in the art would have motivated to provide an azole antifungal agent as its amorphous form in order to increase its solubility and stability in the aqueous coating solutions suggested by the cited prior art.

With regard to claim 17, Applicants argue that while Martindale does recite surfactants for use in pharmaceuticals, it fails to cure the other deficiencies of the cited references. However, Martindale is only provided as evidence that the surfactants recited in claim 17 were known in the art. Gilis et al. teaches that surfactants can be incorporated in pharmaceutical preparations comprising azole antifungal agents.

Accordingly, the claims are deemed properly rejected in view of the teachings of the cited prior art and are maintained for the reasons of record and as reiterated below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 15-16, 18-20, 22-23, and 42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Gilis *et al.*** (WO 00/03697; Published Jan. 27, 2000) and **Ishibashi *et al.*** (U.S. Patent Application Publication No. US 2003/0012815 A1; Published Jan. 16, 2003; Filed Jan. 26, 2001) in view of **Lynenskjold *et al.*** (US 2003/0211168 A1; Published Nov. 13, 2003; Filed Feb. 19, 2001) and ***Nara et al.*** (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997).

The instant claims recite a method of manufacturing a water-insoluble azole antifungal dosing form. Said method comprises a single phase working solution of active agent, water, a water-soluble polymer and a solvent, wherein the solvent is selected from an alcohol, acetone and mixture thereof. The working solution is combined with core particles to produce active agent coated particles.

Gilis *et al.* disclose pellets having a core coated with an antifungal and a polymer (Abstract). With respect to solvents used in forming coated core particles, the reference discloses that dichloromethane and methanol are both Class 2 solvents whose presence in pharmaceutical products should be limited (page 2, lines 28-30). Specifically, the pellets disclosed in Gilis *et al.* comprise: a) a central, rounded or spherical core having a diameter of about 710-1190 μM); b) a coating film of a water-soluble polymer and an antifungal agent; and

c) a seal-coating polymer layer, characterized in that the residual solvent levels in said pellets is within limits set by the ICH, that is, the concentration of dichloromethane is less than 600 ppm, most preferably less than 250 ppm (page 4, lines 24-32). Accordingly, Gilis *et al.* disclose using ethanol as an alcoholic co-solvent that is necessary for applying the drug coat layer to the cores (page 4, lines 34-35), thus meeting the limitations of claim 15. Water-soluble polymers include those recited in instant claim 16, for example, hydroxypropyl methylcellulose, polyvinylpyrrolidones and methacrylates (page 6, line 23 to page 7, line 3). Such polymers are disclosed to have an apparent viscosity of 1 to 100 mPas when dissolved in a 2% aqueous solution, thus reasonably encompassing the limitations of instant claim 4 (page 5, lines 32-34). With respect to the composition of the core particles recited in instant claims 18-19, Gilis *et al.* disclose identical core particles composed of, for example, mannitol or microcrystalline cellulose (page 5, lines 8-19). Preferred antifungal agents for use as drugs in the drug-coating layer are lipophilic azole antifungals, in particular itraconazole (page 7, lines 10-11). The instantly claimed weight ratio of active agent to polymer is obviated by those disclosed at page 7, lines 15-30, for example, 1:1 to 1:5. With respect to the limitations of instant claim 22 wherein an external coating is applied to the drug coated spheres, Gilis *et al.* disclose such an external coating at page 8, lines 28-32. The addition of surfactants as recited in instant claim 3 is disclosed at page 9, lines 1-4. A drying step as recited in claim 1 is disclosed at page 10, lines 32-38).

The reference thus clearly suggests a process of forming drug-coated particles comprising the same steps as those instantly claimed. Further, Gilis *et al.* suggest that the dichloromethane content of the coating should be limited. As such, Gilis *et al.* provide the motivation to use a solvent other than dichloromethane to formulate a coating solution for coating core particles. Gilis *et al.* differ from the claims with respect to the solvents used in the coating solution.

However, Ishibashi *et al.* disclose drug-containing core substance having a multi-layered coating layer (Abstract). With respect to the coating solution used to coat the disclosed core particles, the reference discloses that the solvent system should dissolve both the hydrophobic organic compound and water-soluble polymer (page 6, ¶ [0057]). Suitable solvents include alcohols such as ethanol as well as ketones such as acetone (*id.*). The reference thus teaches that

ethanol and acetone are suitable solvents for applying a coating solution to a core particle. The reference does not teach coating solutions additionally comprising water as instantly claimed.

However, Lynenskjold *et al.* teach a process for the production of drug carrier pellets comprising spray-drying a solution of a physiologically tolerable cellulosic binder containing an active drug (Abstract; Example 5). With respect to active drug substances coated onto the spray-dried pellets, the inventors teach that the antifungal, ketoconazole, as recited in claim 42, is one such active drug substance (page 4, [0046]). The active drug substance will generally be applied to the spray-dried pellets in the form of a solution or dispersion in a physiologically tolerable solvent or solvent mixture, optionally incorporating other components such as binders, sweeteners, pH modifiers, antioxidants, etc. (page 4, [0050]). The coatings may also include further components, including antiadhesives, which are reasonably interpreted as surfactants as recited in claims 3 and 17 (page 5, [0057]). With respect to the coating solutions, while the use of aqueous solutions or dispersions is preferred, organic solvents such as ethanol and acetone as recited in the instant claims may also be used (page 5, [0058]). Methylene chloride, as taught in Gilis *et al.* cited *supra*, may be used but is generally not preferred (*id.*).

Similarly, Nara *et al.* teach solvents for coating solutions may be water, an organic solvent, or mixtures thereof (col. 6, lines 34-35). The organic solvent may be any organic solvent capable of dissolving a water-insoluble substance, such as ethanol or acetone as recited in the instant claims (col. 6, lines 38-46). Water and its mixture with an organic solvent are "preferably used as solvent of coating composition" (col. 6, lines 47-48).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use any suitable solvent system, especially an aqueous-based solvent system, to provide a working solution for coating core particles. In the instant case, the skilled artisan would have been imbued with at least a reasonable expectation that a solvent system consisting of water and alcohol or acetone or mixtures thereof would be effective in dissolving both a water-soluble polymer as well as a hydrophobic active agent such as ketoconazole. The Examiner also notes that acetone is well known in the art as an organic solvent suitable for dissolution of organic compounds. Further, coating core particles with an active agent is a well-known process as evidenced by the cited references. Applicants' process of coating such particles differs from Gilis *et al.* in the composition of the working solution. However, as

discussed *supra*, modifying the working solution of Gilis *et al.* so as to provide dissolution of both a hydrophobic active agent and a water-soluble polymer, while at the same time eliminating methylene chloride from the solution, would require nothing more than identification of solvents suitable for such a purpose. To this point, Ishibashi *et al.* disclose that acetone and ethanol are solvents that may effectively dissolve both hydrophobic organic compounds and water-soluble polymers. Further, Lynenskjold *et al.* and Nara *et al.* both teach that aqueous solutions or aqueous solutions containing an additional organic solvent such as ethanol or acetone are suitable for use in coating core particles. Gilis *et al.* and Lynenskjold *et al.* provide the motivation to use a solvent other than dichloromethane wherein they disclose that the dichloromethane content of the coating should be limited.

With respect to instant claim 2, which recites that the pH of the working solution is adjusted to solubilize the active agent, such a method step would have been obvious to the skilled artisan. For example, many drugs have pH-dependent solubility. As such, if the drug being dissolved in the working solution is insoluble at the pH of the solution, the skilled artisan would be motivated to adjust the pH so as to fully solubilize the active agent. Further Lynenskjold *et al.* teaches that a pH modifying agent may be added to the coating solution disclosed therein.

With respect to instant claim 6, which recites specific ratios of water to working solution, it is well within the level of ordinary skill in the art to determine optimal working ranges of prior art processes and compositions. As such, because an aqueous-based coating solution is *prima facie* obvious as discussed *supra*, determining the optimum ratio of water to, for example, ethanol or acetone in such coating solutions, would require no more than routine optimization.

Accordingly, the claims are deemed properly rejected as being obvious over Gilis *et al.* and Ishibashi *et al.* in view of Lynenskjold *et al.* and Nara *et al.* who provide the teaching, suggestion and motivation to use any suitable solvent system in order to provide a working solution for coating core particles. Coating core particles with azole antifungal active agent containing coating solutions was clearly well known in the art as evidenced by Gilis *et al.* In fact, the only difference between the prior art and the claims is the composition of the coating solution used to dissolve a water-soluble polymer and azole antifungal agent. However, when the prior art is viewed as a whole, it would have been obvious to one of ordinary skill in the art

that the coating solution used to spray coat core-particles could be readily modified by using different solvent systems. The skilled artisan would have been imbued with at least a reasonable expectation that any solvent system capable of dissolving a hydrophobic drug and water-soluble polymer would be effective for spray coating a drug onto core particles and would have been highly motivated to try different combinations of solvents for such a purpose, especially solvents and solvent systems that were known to dissolve both hydrophobic organic compounds and water-soluble polymers as taught in Ishibashi *et al.*, Lynenskjold *et al.,* and Nara *et al.*.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Gilis *et al***. (WO 00/03697; Published Jan. 27, 2000), **Ishibashi *et al***. (U.S. Patent Application Publication No. US 2003/0012815 A1; Published Jan. 16, 2003; Filed Jan. 26, 2001), **Lynenskjold *et al***. (US 2003/0211168 A1; Published Nov. 13, 2003; Filed Feb. 19, 2001), and ***Nara et al***. (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997) as applied to claims 1-6, 15-16, 18-20, 22-23, and 42 above, and further in view of **Vladyka *et al***. (USP No. 6,497,905 B1; Issued Dec. 24, 2002; Filed Mar. 20, 2000).

Gilis *et al*., Ishibashi *et al*., Lynenskjold *et al*., and Nara *et al*. teach as applied *supra* and are here applied to claim 7 in the same manner. The references do not teach the amorphous form of an azole antifungal agent as recited in claim 7.

However, Vladyka *et al*. teach that members of the class of azole antifungal agents such as ketoconazole and itraconazole have very low solubility in aqueous media and will benefit from the method of conversion to the amorphous state (col. 5, lines 36-43).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to provide the claimed azole antifungal agent in the amorphous state because Vladyka et al. teach that these agents having low aqueous solubility will benefit from providing them in their amorphous state. The skilled artisan would reasonably expect that an azole antifungal agent in its amorphous state will exhibit increased solubility (Vladyka et al., col. 5, lines 20-25) in the aqueous coating solutions as motivated and suggested by Gilis *et al*., Ishibashi *et al*., Lynenskjold *et al*., and Nara *et al*. as discussed *supra*.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Gilis *et al.*** (WO 00/03697; Published Jan. 27, 2000), **Ishibashi *et al.*** (U.S. Patent Application Publication No. US 2003/0012815 A1; Published Jan. 16, 2003; Filed Jan. 26, 2001), **Lynenskjold *et al.*** (US 2003/0211168 A1; Published Nov. 13, 2003; Filed Feb. 19, 2001), and ***Nara et al.*** (USP No. 6,245,351 B1; Issued Jun. 12, 2001; Filed Mar. 4, 1997) as applied to claims 1-6, 15-16, 18-20, 22-23, and 42 above, and further in view of **Martindale: The Complete Drug Reference** (Pharmaceutical Press, London, 2002, pages 1344-1349).

Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* teach as applied *supra* and are here applied to claim 7 in the same manner. The references do not teach the specific surfactants as recited in claim 17.

However, Martindale teaches that surfactants are compounds that can reduce the interfacial tension between two immiscible phases (page 1344), specifically teaching that polysorbates (20, 40, 60, and 80), polyoxyl castor oils, poloxamers, and sorbitan esters (*e.g.*, sorbitan laureate, sorbitan palmitate, and sorbitan stearate) are suitable for use as surfactants in the manufacture of pharmaceuticals (pages 1346-1349).

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use any known surfactant, such as those taught by Martindale, in the manufacture of azole antifungal-coated particles. Gilis *et al.* teach that surfactants can be incorporated in pharmaceutical preparations comprising azole antifungal agents. As such, the skilled artisan would have been imbued with at least a reasonable expectation that the surfactants taught in Martindale would be amiable for use in the coating methods suggested and motivated by the cited references.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614